# Tuning the Kinetics of Cadherin Adhesion

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Cadherins are $Ca^{2+}$-dependent cell–cell adhesion proteins that maintain the structural integrity of the epidermis; their principle function is to resist mechanical force. This review summarizes the biophysical mechanisms by which classical cadherins tune adhesion and withstand mechanical stress. We first relate the structure of classical cadherins to their equilibrium binding properties. We then review the role of mechanical perturbations in tuning the kinetics of cadherin adhesion. In particular, we highlight recent studies that show that cadherins form three types of adhesive bonds: catch bonds, which become longer lived and lock in the presence of tensile force; slip bonds, which become shorter lived when pulled; and ideal bonds, which are insensitive to tugging.

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## INTRODUCTION

The epidermis serves as a physical barrier that protects organisms from their external environment. This multilayered tissue is composed of keratinocytes bound together by two types of cell–cell adhesion complexes: desmosomes and adherens junctions (Jensen and Wheelock, 1996). The primary adhesive components of both these structures are the cadherin family of $Ca^{2+}$-dependent transmembrane proteins (Gumbiner, 2005; Halbleib and Nelson, 2006; Green and Simpson, 2007; Al-Amoudi and Frangakis, 2008; Niessen *et al.*, 2011). Desmosomes are composed of two types of desmosomal cadherins (desmocollin and desmoglein) (Green and Simpson, 2007; Desai *et al.*, 2009), whereas epidermal adherens junctions contain a single classical type-1 cadherin (either E-cadherin or P-cadherin) (Jensen and Wheelock, 1996; Halbleib and Nelson, 2006). Both desmosomes and adherens junctions act in a coordinated manner to help the epidermis withstand mechanical stress. Although the interactions that mediate desmosomal cadherin binding are not completely understood, the structural basis of classical cadherin adhesion has been extensively characterized.

Classical cadherins share a conserved cytoplasmic domain, and an ectodomain containing five tandem extracellular (EC) repeats. Their expression levels vary within the epidermis; although E-cadherins are present in all keratinocytes, expression of P-cadherins is limited to the basal layer (Takeichi, 1988; Halbleib and Nelson, 2006). Adhesion is mediated by the cadherin ectodomain, whereas the cytoplasmic region binds to adaptor proteins that link cadherins indirectly to the cytoskeleton, regulate cadherin turnover, and modulate actin assembly (Nelson and Nusse, 2004; Takeichi, 2007; Niessen *et al.*, 2011). As the epidermis is a self-renewing tissue with a continuous upward movement of cells, cadherins dynamically tune their adhesive strength in order to preserve epidermal barrier integrity (Niessen, 2007). Epidermal cadherin–knockout studies in mice show that loss of E-cadherin correlates with a loss of adherens junctions, altered epidermal differentiation, and loss of hair follicles (Young *et al.*, 2003; Tinkle *et al.*, 2004). Similarly, deletion of α-catenin, an adaptor protein associated with the cadherin cytoplasmic domain, results in impaired adhesion and epidermal detachment (Vasioukhin *et al.*, 2001).

Cell–cell adhesion is a dynamic process, and classical cadherins tailor their binding kinetics in order to withstand mechanical perturbations. While the equilibrium binding properties of classical cadherins have been extensively characterized (Brasch *et al.*, 2012), the role of mechanical force in altering cadherin binding is only now being measured. Recent studies show that upon being exposed to mechanical perturbation, E-cadherins change their unbinding kinetics (Rakshit *et al.*, 2012). These kinetic changes are not manifested in solution or in the absence of mechanical loading, but are critical for cadherin adhesion.

This brief review summarizes our current understanding of the effect of mechanical force on the kinetics of E-cadherin adhesion. We focus on the ectodomain; the role of the cytoplasmic domain and its associated proteins has been reviewed elsewhere (Schwartz and DeSimone, 2008; Papusheva and Heisenberg, 2010; Gomez *et al.*, 2011; Leckband *et al.*, 2011; Ladoux and Nicolas, 2012). We begin by relating the structure of E-cadherins to their equilibrium binding properties. We then review the role of mechanical perturbations in tuning the kinetics of adhesion. Finally, we discuss major open questions and future directions in this exciting area of research.

## ADHESIVE STATES OF CLASSICAL CADHERINS

Classical cadherins adhere via ''*trans*'' interactions where ectodomains from opposing cells bridge the inter-membrane gap and interact with each other. Adhesion is strengthened by the cooperative self-assembly of cadherins on the same cell into *cis* clusters (Brasch *et al.*, 2012).

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*Abbreviations: EC, extracellular; WT, wild-type*

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### Structure and kinetics of *trans*-adhesive states

Structural studies of both the complete ectodomain of type-I classical C-cadherin (EC1–5) (Boggon *et al.*, 2002) and of smaller fragments of E-Cadherin and N-Cadherin (Shapiro *et al.*, 1995; Nagar *et al.*, 1996; Pertz *et al.*, 1999; Haussinger *et al.*, 2004; Harrison *et al.*, 2010) have identified key interactions that mediate *trans* adhesion (Figure 1). The primary adhesive conformation involves the interaction of opposing EC1 domains and is termed the strand-swapped dimer (Figure 1a). In this structure, N-terminal β-strands between opposing EC1 domains are swapped, and the side chain of a conserved tryptophan at position 2 (W2) is inserted into a pocket on their adhesive partner (Shapiro *et al.*, 1995; Boggon *et al.*, 2002; Haussinger *et al.*, 2004; Parisini *et al.*, 2007) (Figure 1a). The physiological relevance of this adhesive interface has been confirmed in numerous mutational, structural, and cellular studies (Tamura *et al.*, 1998; Pertz *et al.*, 1999; Troyanovsky *et al.*, 2003; Shan *et al.*, 2004; Harrison *et al.*, 2005; Prakasam *et al.*, 2006a). In solution, the affinity for strand-swap dimer formation is low; dissociation constants ($K_d$) for *trans* dimers of the full-length ectodomain of C-cadherin measured using analytical ultra centrifugation is 64 μM (Chappuis-Flament *et al.*, 2001). Similarly, EC1–2 domains of E-cadherin expressed in mammalian and bacterial cells have *trans*-dimer $K_d$ values of 97 μM (Katsamba *et al.*, 2009) and 80 μM (Koch *et al.*, 1997), respectively.

Before strand swapping, cadherin monomers are in a "closed" conformation where W2 is docked into each monomer's binding pocket; the monomers thus act as competitive inhibitors of strand swapping (Chen *et al.*, 2005). The closed monomeric conformation places a strain on the short swapping strand owing to its anchorage at one end by the W2 and at the other by a $Ca^{2+}$ ion; relieving this conformational strain is the driving force for strand swapping (Vendome *et al.*, 2011). Equilibrium affinity measurements using analytical ultra centrifugation show that mutations that relieve strain in the swapping strand in E-cadherin monomers decrease dimerization affinities (Vendome *et al.*, 2011). Single-molecule fluorescence resonance energy transfer experiments suggest that before swapping N-terminal β-strands, E-cadherin monomers first form a non-swapped, intermediate "encounter complex" (Figure 1c) (Sivasankar *et al.*, 2009). E-cadherins can be trapped in this encounter complex by mutating W2 (Sivasankar *et al.*, 2009); consequently, W2A fragments weakly adhere to each other (Prakasam *et al.*, 2006a; Sivasankar *et al.*, 2009). Recently, the atomic resolution structure of the encounter complex has been resolved in W2A mutants (Figure 1b). This conformation, called an X-dimer, is formed by extensive surface interactions between the base of the EC1 domain, EC1–2 interdomain linker region, and the apex of domain EC2 (Harrison *et al.*, 2010) (Figure 1b). The affinity for X-dimer formation in solution is

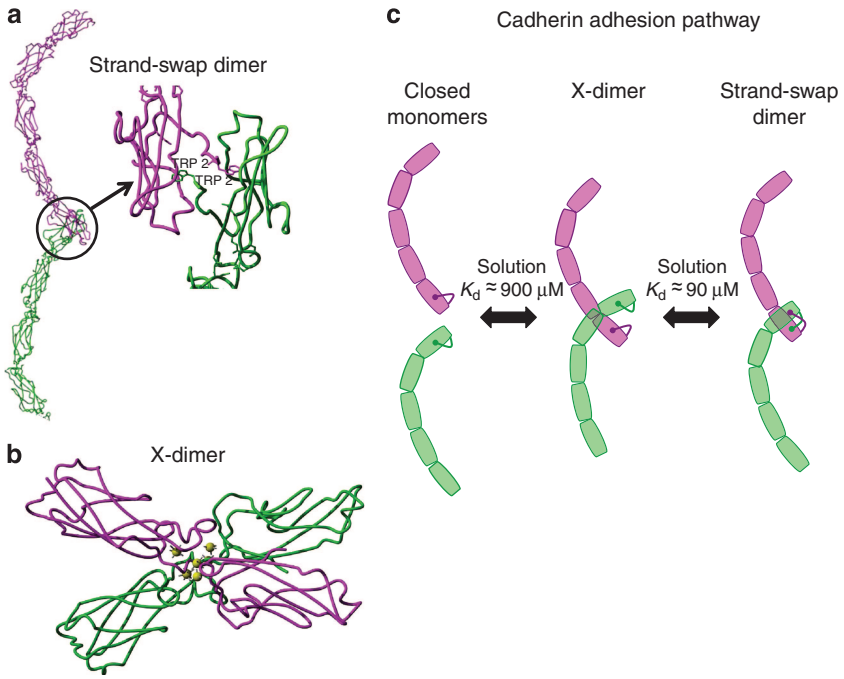


**Figure 1. Adhesive states of classical cadherin and the pathway for cadherin binding.** (**a**) The extracellular region of type-I classical cadherin is composed of five tandem extracellular (EC) domains. Linkers between successive EC domains are each bound to three $Ca^{2+}$ ions, which give the ectodomain its characteristic curvature. Ectodomains from opposing cells (shown in green and magenta) adhere across the inter-membrane gap via "*trans*" interactions. The primary *trans* interface involves the interaction of opposing EC1 domains and is termed the strand-swapped dimer. In this conformation, N-terminal β-strands between opposing EC1 domains are swapped, and the side chain of a conserved tryptophan at position 2 (W2) is inserted into a pocket on their adhesive partner. (**b**) Before strand swapping, cadherin ectodomains form a non-swapped, intermediate conformation called an X-dimer. This conformation is formed by extensive surface interactions between the base of the EC1 domain, EC1–2 inter-domain linker region, and the apex of domain EC2. (**c**) Cadherin monomers adopt a "closed" conformation where W2 is docked into each monomer's binding pocket. Monomers from opposing cells interact to form X-dimers and then proceed to swap W2 residues to form a strand-swap dimer. The $K_d$ of the EC1–2 domains of W2A E-cadherin X-dimers is 916 μM (Harrison *et al.*, 2010), whereas the $K_d$ of the EC1–2 domains of wild-type E-cadherin strand-swap dimers is 97 μM (Katsamba *et al.*, 2009).

significantly weaker than strand-swap dimers; the $K_d$ of W2A cadherin X-dimers is an order of magnitude higher (916 μM) than wild-type (WT) cadherin strand-swap dimers (Harrison *et al.*, 2010).

Mutations in the cadherin X-dimer–binding interface alter the kinetics of strand swapping but do not change the structure of the strand-swap dimer. When a key Lys 14 residue in the X-dimer-binding interface is mutated to a Glu, the *trans* dimers are virtually indistinguishable from WT cadherin strand-swap dimers (Harrison *et al.*, 2010). As measured using surface plasmon resonance, the K14E mutants show no binding in a short time frame, suggesting that their binding rate (on-rate) is low. Similarly, sedimentation velocity analytical ultra centrifugation and size-exclusion chromatography show that the monomer to strand-swap dimer conversion is impeded in these mutants (Harrison *et al.*, 2010). Presumably, lower on-rates are measured, as the formation of X-dimers, which serve as kinetic intermediates during strand swapping (Figure 1c), are impaired in the K14E mutants. In epithelial cells, inactivation of X-dimers result in extraordinarily stable cell–cell junctions; this has been interpreted to indicate that X-dimers are an intermediate in the pathway to dissociation of strand-swap dimers (Hong *et al.*, 2011). Analytical ultra centrifugation measurements show that the $K_d$ of the K14E mutants are virtually indistinguishable from WT cadherin, which suggests that besides their low on-rate, the dissociation (off-rate) of these mutants is also decreased (Harrison *et al.*, 2010). However, in contrast to these studies, recent single-molecule force measurements indicate that the dissociation rate of K14E is similar to WT cadherin (Rakshit *et al.*, 2012). Consequently, the molecular role of X-dimers in the dissociation of strand-swap dimers is unclear.

### Structure and kinetics of *cis*-adhesive states

Cadherin adhesion is enhanced by their lateral assembly on the cell surface (Takeda *et al.*, 1999; Kim *et al.*, 2005). However, the biophysical mechanisms by which *cis* clustering boosts adhesion are just beginning to be understood. Early studies showed that beads decorated with cadherin pairs aggregated to a greater extent than beads with immobilized monomers (Brieher *et al.*, 1996). Although these data were interpreted to suggest that cadherin ectodomains form *cis* dimers, recent single-molecule experiments show that ectodomains located adjacent to each other cooperatively enhance the probability of adhesion even if they do not associate with each other in a *cis* geometry (Zhang *et al.*, 2009).

On the basis of contacts observed in X-ray crystal structures of a range of classical cadherins, it has been proposed that interactions between the apex of EC1 and the base of EC2 of neighboring cadherins mediate dimerization in a *cis* orientation (Boggon *et al.*, 2002; Harrison *et al.*, 2011). These interactions are, however, not observed in nuclear magnetic resonance measurements of EC1–2 (Haussinger *et al.*, 2002), indicating that their $K_d$ exceeds 1 mM (Harrison *et al.*, 2011). Similarly, single-molecule fluorescence resonance energy transfer experiments could not detect *cis*-dimer formation between two cadherin ectodomains that were located adjacent to each other in a configuration that would permit lateral dimerization (Zhang *et al.*, 2009). This discrepancy is explained by recent theoretical studies, which predict that the *cis* assembly of cadherin ectodomains requires prior *trans* dimerization (Wu *et al.*, 2010, 2011). When *trans* dimers are formed, the conformational flexibility of ectodomains is markedly reduced, which lowers the entropic penalty associated with *cis*-dimer formation (Wu *et al.*, 2011).

In qualitative agreement with these predictions, micropipette manipulation experiments show that the binding of cadherins from opposing cells occurs in two stages: an initial rapid stage ascribed to *trans* adhesion, followed by a second slower stage interpreted to occur owing to *cis* clustering (Chien *et al.*, 2008). However, although the first stage requires the EC1 domain as expected for *trans*-dimer formation, EC3 is required for the second adhesive state (Chien *et al.*, 2008). Micropipette experiments also demonstrate that hypoglycosylation of EC2 and EC3 enhance the lateral assembly of ectodomains (Langer *et al.*, 2012).

## MECHANICAL TENSION ALTERS THE KINETICS OF CADHERIN ADHESION

The structural and biophysical studies described above provide a detailed picture of the kinetic determinants of classical cadherin binding in equilibrium, under force-free conditions. However, the molecular mechanisms by which cadherins alter their binding kinetics in response to mechanical forces are still unclear.

When cadherin *trans* dimers are pulled apart, they can form one of three distinct types of bonds (Dembo *et al.*, 1988; Dembo, 1994): (i) Slip bonds, which weaken and have a higher off-rate when pulled; (ii) Catch bonds, which counter-intuitively strengthen such that their off-rates decrease; and (iii) Ideal bonds, which are unaffected by mechanical stress. Slip bonds are the most commonly observed interactions in biology. Catch bonds provide a way for the interacting proteins to grip tightly in the presence of tugging forces. Finally, although ideal bonds were theoretically proposed more than a decade ago (Dembo *et al.*, 1988; Dembo, 1994), they had not been experimentally observed in any biological system.

Recently, single-molecule atomic force microscope force measurements were used to show that E-cadherins form bonds with catch, slip, and ideal mechanical properties (Rakshit *et al.*, 2012). The lifetimes of E-cadherin-binding conformations were measured as they were subjected to different pulling forces. These experiments showed that although W2A mutant X-dimers formed catch bonds, WT and K14E strand-swap dimers formed slip bonds (Rakshit *et al.*, 2012) (Figure 2a and b). WT cadherins were also shown to form ideal bonds, which were hypothesized to arise as X-dimers converted to a strand-swap conformation (Figure 2b) (Rakshit *et al.*, 2012).

### X-dimers form catch bonds

When X-dimers were tugged, their bond lifetimes increased with force, indicative of a catch bond. After reaching a

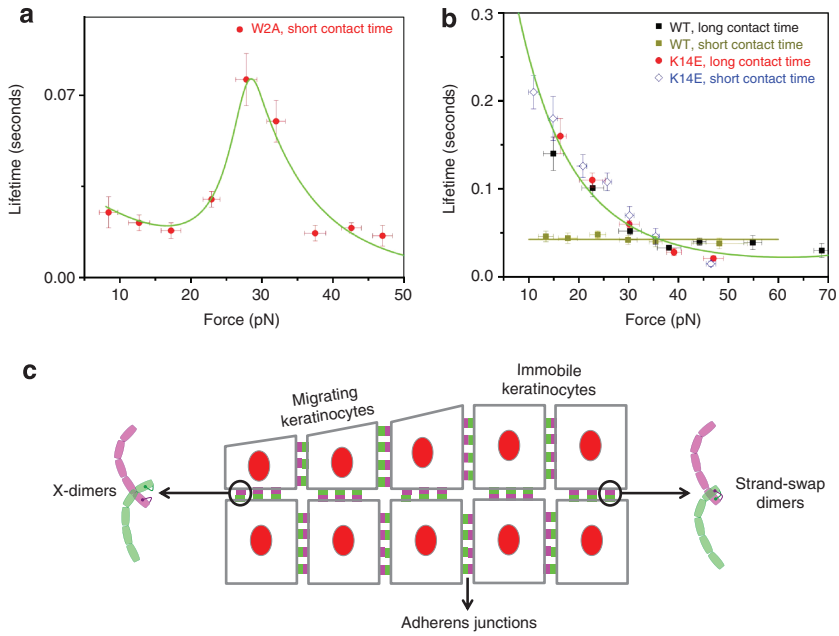


**Figure 2. Mechanical force tunes the kinetics of cadherin adhesion.** Adapted from Rakshit *et al.* (2012). (**a**) X-dimers form catch bonds, which become longer lived and lock in the presence of tensile force. When W2A cadherin X-dimers are pulled, their bond lifetimes increase with force. After reaching a maximum at a critical force of ~30 pN, the lifetimes decrease. (**b**) Strand-swap dimers form slip bonds, which become shorter lived when pulled. Slip bonds are formed by K14E mutants that interact for short and long periods of time and also by wild-type (WT) cadherins that interact for long periods of time. However, when WT cadherins interact for a short period of time, they form ideal bonds that are insensitive to force. (**c**) Hypothetical mechanism by which keratinocytes resist tensile forces during skin renewal and wound healing. As skin cells reposition themselves, E-cadherins bind rapidly to form X-dimers that allow cells to grip strongly under load. In immobile keratinocytes, E-cadherins form more robust strand-swap dimers that have a high affinity in the absence of force.

maximum at a critical force of ~30 pN, the lifetimes decreased with force (Figure 2a). A similar behavior was measured when WT cadherins were forced into an X-dimer conformation by competitively inhibiting strand swapping using free W in solution (Rakshit *et al.*, 2012). X-dimer catch bonds are observed because the cadherins reorient when they are pulled such that they form transient, force-induced bonds and lock more tightly.

Although this was the first observation of catch bonds in cadherin adhesion, these bonds have previously been measured with other adhesive proteins such as selectins (Marshall *et al.*, 2003; Sarangapani *et al.*, 2004; Yago *et al.*, 2004), FimH (Thomas *et al.*, 2002; Le Trong *et al.*, 2010), and integrins (Kong *et al.*, 2009). Although it is tempting to speculate that the physiological role of X-dimer catch bonds is to allow cells to grip tightly and lock in place when pulled, this hypothesis remains to be tested.

### Catch bonds resolve discrepancies between solution and surface force measurements

Over a decade ago, surface force apparatus measurements of the interactions between cadherin ectodomains immobilized on lipid membranes suggested that classical cadherins bind in three distinct conformations (Sivasankar *et al.*, 2001). The weakest conformation required W2, and corresponded to a strand-swapped dimer (Zhu *et al.*, 2003; Prakasam *et al.*, 2006b). The second conformation had an intermediate binding strength and required EC1 – 2 (Zhu *et al.*, 2003); based on recent structural data, it is likely that this adhesive state corresponds to the X-dimer complex. The third and strongest adhesion required the EC3 domains to interact directly (Zhu *et al.*, 2003); although this adhesive state likely corresponds to a *cis*-dimer structure, this remains to be confirmed. Single-molecule atomic force microscope force measurements of the interaction of different classical cadherins confirmed the results of the ensemble surface force apparatus measurements (Perret *et al.*, 2004; Bayas *et al.*, 2006; Shi *et al.*, 2008, 2010).

It was initially believed that the surface force apparatus measurement of stronger adhesion between X-dimers compared with strand-swap dimers directly contradicted the results of solution affinity measurements, which showed that X-dimers have higher off-rates than strand-swap dimers. However, the discovery of X-dimer catch bonds resolves this apparent discrepancy (Figure 2a). As catch bonds strengthen in the presence of force, X-dimer adhesion, which is weak in the absence of force, becomes stronger when pulled.

### Strand-swap dimers form slip bonds

As strand-swap dimers have a higher binding affinity than X-dimers (Katsamba *et al.*, 2009; Harrison *et al.*, 2010), WT cadherins form strand-swap dimers when they interact for long periods of time. Single-molecule atomic force microscope force-clamp experiments showed that these WT cadherin strand-swap dimers formed slip bonds; their bond lifetimes decreased with increasing tensile force (Figure 2b). Not surprisingly, identical slip bonds were formed by the K14E strand-swap dimers (Rakshit *et al.*, 2012) (Figure 2b). The

intrinsic off-rate of both the WT E-cadherin and K14E strand-swap dimers was $1.6\,s^{-1}$ (Rakshit *et al.*, 2012), which is similar to an off-rate of $0.7\,s^{-1}$ measured for WT E-cadherins using nuclear magnetic resonance (Haussinger *et al.*, 2004).

**Ideal bonds are formed as X-dimers transition to a strand-swap conformation**

Besides forming catch and slip bonds, cadherins also form ideal bonds that behave like mechanical dampers and prevent the abrupt jolting of cells. When WT cadherin interaction time was decreased, the lifetimes of their interactions were independent of force; they formed ideal bonds (Rakshit *et al.*, 2012) (Figure 2b). It was hypothesized that ideal bonds correspond to an intermediate state that is formed when X-dimers transition to strand-swap binding (Rakshit *et al.*, 2012). However, the structure of the intermediate state and the molecular contacts responsible for ideal bond formation still need to be resolved.

## FUTURE DIRECTIONS

Catch, slip, and ideal bonds suggest a physical mechanism that E-cadherins use to resist tensile force as cells rearrange during skin renewal and wound healing. It is tempting to speculate that as keratinocytes reposition themselves, E-cadherins bind rapidly to form X-dimer catch bonds that allow cells to grip strongly under load (Rakshit *et al.*, 2012) (Figure 2c). Over time, the X-dimers proceed to form more robust strand-swap dimers that have a high affinity in the absence of force (Figure 2c); this conversion is facilitated by an intermediate conformation that is insensitive to tensile force (Rakshit *et al.*, 2012). However, it is currently unclear whether keratinocytes use such a mechanism to tune adhesive properties. Studying cadherin bond mechanics in living cells will be a crucial first step to addressing this question.

Besides mediating robust adhesion, classical cadherins have a key role in mechanotransduction by sensing physical stimuli at cell–cell junctions, transmitting them to the cytoplasm, and activating a biochemical response (Ladoux *et al.*, 2010; le Duc *et al.*, 2010; Liu *et al.*, 2010; Weber *et al.*, 2012). It is believed that cadherins along with their adaptor proteins, β-catenin and α-catenin, form the core force-bearing unit in the transmission of mechanical signals (Leckband *et al.*, 2011). To accomplish this, it is critical that the interactions between cadherins and catenins remain intact when exposed to force. However, the force-dependent binding kinetics of these interactions have not yet been studied. Furthermore, the role of these adaptor proteins in altering cadherin mechanical properties is still an open question. For instance, it is known that the adaptor protein α-catenin has an important role in strengthening cadherin bonds following initial adhesion (Bajpai *et al.*, 2008). Whether α-catenin and other adaptor proteins alter the force-dependent kinetics of cadherin bonds needs to be investigated.

Some of the discrepancies in cadherin binding measured using solution affinity measurements and force measurements arise owing to differences between cadherin interactions in solution, under force-independent conditions, and cadherin adhesion in the presence of mechanical stress. The discovery that cadherins vary their lifetimes in response to force reconciles some of these differences (Rakshit *et al.*, 2012). However, several open questions remain. For instance, the molecular interactions by which cadherins form catch bonds are not known. Furthermore, the hypothesis that ideal bonds correspond to an intermediate state, which is formed as cadherin X-dimers transition to a strand-swap conformation, needs to be tested at the molecular level. Finally, the role that X-dimers have in the dissociation of strand-swap dimers is unclear.

## CONFLICT OF INTEREST

The author states no conflict of interest.

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